PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of an intensive 3-week preoperative home rehabilitation programme in chronic obstructive pulmonary disease patients eligible for lung cancer surgery: A multicentre randomized controlled trial
AUTHORS	Laurent, Hélène; Galvaing, Géraud; Thivat, Emilie; Coudeyre, Emmanuel; Aubreton, Sylvie; Richard, Ruddy; Kwiatkowski, Fabrice; Costes, Frederic; Filaire, Marc

VERSION 1 – REVIEW

REVIEWER	Sâmia Geórgia Dantas Linhares Heart Institute (InCor) São Paulo Brazil
REVIEW RETURNED	14-May-2017

GENERAL COMMENTS	The question is valid and important, I am curious what the results would be. In the text, with the exception of 1st, 6th and 11th days that will be supervised sessions, there is no information if the other days of training will be free choice of patients or if the study will determine the days. Will upper limb exercises be performed on the same days as high intensity training? if yes, after or before? How will the load be determined? What exercises will be performed? What will be the number of repetitions and sets of the exercise?

REVIEWER	Vinicius Cavalheri School of Physiotherapy and Exercise Science, Curtin University, Australia
REVIEW RETURNED	19-Jun-2017

GENERAL COMMENTS	The study is novel, relevant to the field and I would strongly recommend the publication of the protocol. However, some modifications are needed to improve the quality of the protocol. Further, although the authors have stated that the English language has been verified by a native English translator, the authors should seek feedback from a native English speaker. Some sentences may have either lost their meaning during the translation process.

	One example is (page 9): “We will record the number of realized exercise session(s) effected, the number of exercise session(s) not effected and the reason(s) why they were not effected”. Introduction The gap in the literature was identified. However, some sentences in the introduction are vague and lack further explanation. Additionally, in several instances it is hard to the reader to understand the link between sentences. For instance, the flow of ideas presented between lines 22 and 48 can be improved by further explanation of thoughts as well as by using linking words to connect sentences. I have made some English language suggestion under “Specific comments”. Can the authors give a reason for why “only 25% of patients are considered suitable for surgery” (line 14; page 4)? The aim stated at the end of the introduction does not match the aim stated in the abstract. The authors should state an aim that reflects their population, intervention and main outcomes. My suggestion is: “in people with lung cancer and COPD who are eligible for lung resection, to investigate the effectiveness of a home-based preoperative exercise training program on hospital discharge ability and postoperative complications”. Methods The methods are reasonably well described. The inclusion criteria are clear and specific. However, there is no need to state “>18 years old” as people are usually diagnosed with COPD when they are >40 years of age. The first two “non inclusion criteria” are redundant as they are the opposite of two inclusion criteria. People undergoing either lobectomy of pneumonectomy will be eligible for inclusion. What is not clear is the type of surgical approach. Will the study include people following VATS only, open thoracotomy only or either of these approaches? Can the authors explain why the study will not include people living alone? Can the authors clarify what they mean by “number of peaks”? The meaning of the term might have been lost with the translation to English language. With respect to the muscle strengthening exercises for upper limbs using elastic bands, can the authors provide more details (i.e. how the intensity will be prescribed, how many days/week, which muscle groups will be the focus of the exercise prescription, sets, repetitions…) ? How will the authors measure adherence to the exercise intervention? Will patients be given a diary? Will the authors ring participants on a daily/weekly basis? The authors will be conducting an impressive number of assessments. What is not clear is the number of assessment days that will be required at each evaluation period.

	Can the authors give specific details of number of assessment days, which assessments will be performed on the same day and what is the rest period between one assessment day and the next? The concern is the high burden all these assessment will have on participants of the study. Hospital discharge ability: was the 10-item list developed by the research group? Is it currently used in the 4 hospitals where participants will be recruited from? Has it been validated? For all outcome measures described, please include the devices that will be used to measure them as well as the devices' model and manufacturer details. If data from PFT, maximal respiratory pressures, CPET, 6MWT and quads strength will be presented using absolute values as well as a percentage of predicted values, please provide references for the studies in which the predicted values have been published. CPET - What will be the initial workload? What about the workload for the one-minute increments? 6MWT – It is well known that the 6MWT has a learning effect. Will the participants undergo 2 6MWT's during the first evaluation period? If so, how long will they rest between the first and second 6MWT? Randomization and allocation – The randomization sequence should be generated/managed by someone who is not involved in the research. Not by the research manager. Also, can the authors give more details about the allocation concealment? Discussion Can the authors elaborate more on the mechanism behind decreased postoperative complications and length of stay due to improvements in preoperative exercise capacity? That is, why would an improvement in preoperative exercise capacity lead to improved postoperative outcomes? Specific comments and English language tips Abstract: Conclusion – Delete "the" from "We hypothesize … will increase the aerobic capacity" Introduction: Page 4 (line 9): "surgery is conducted in a curative intent" – replace "in" with "with"; (line 11): "early TNM disease stages (stages I and II)" – include (stages I, II and IIIA); (line 27): "Patients with complicated postoperative course have a longer hospital length of stay, a more frequent stay in intensive care unit (ICU) and a higher mortality rate" – please include reference for this statement; (line 33): "Field tests are…" include "Performance during field-based tests are…"; (line 37): "Surgery itself initiates…" replace "initiates" with "leads to". Page 5 (line 5): "Two recent systematic reviews reported…", please have a look at a recently published Cochrane review on preoperative exercise training in people with lung cancer;

	Methods: Page 8 (line 33): “The Rehabilitation group will realize…” – replace “realize” with “undergo”; (line 55): “ability to complete his training course and to teach him” – replace “his” with “their” and replace “him” with “them”. Page 11 (line 50): “It will be realized…” – replace “realized” with “performed” Page 14 (line 9): “… those who realize…” – replace “realize” with “attended”. Page 16 (line 3): “This analysis will be performed intent-to-treat” – reword to “This analysis will be performed according to the intention-to-treat principle”.

REVIEWER	Raquel Sebio School of Health Sciences. Tecnocampus Mataró-Maresme. Pompeu Fabra University
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	This is a very interesting study which will address very important outcomes for clinical practice in patients with lung cancer. One of the strengths of this research piece is the elevated number of patients which will be recruited (over 90) and the fact that it will be short (three weeks) and minimally supervised (one session at the hospital two unsupervised at home) which will probably improve the recruitment rate and completion rate (which is usually pretty low in this type of patients). However, at the moment the study present some limitations that must be addressed before acceptance. For starters, the authors say that the English has been proofread by a native speaker but I strongly disagree since I have noticed several grammatical mistakes and some sentences and even paragraphs should be rewritten. For example, in the abstract it says "was shown" instead of have shown; they also used somewhere realized instead of performed; the article "the" is constantly used when it shouldn't be, and so on. More examples of this can be found in page 4 line 16 and 26-27; in the inclusion criteria it should read predicted not theoretical; page 8 line 44; page 9 lines 20 to 25... Also, they are apparently writing in British English but some other words such as dyspnoea and post-operative complications are written correspond to American English. Please unify. There are also several aspects that must be clarified: -When the authors say contraindication to perform CPET could they be more specific? -The standard care should be described in detail. For instance, they say global training what does that mean? Endurance training? Which type/intensity/frequency....? -More information is needed regarding surgery. What approach is going to be performed? This should also be stated because it will affect the post-operative course.

	With regard to the methodology, I don't understand why the authors say that this can't be an assesir-blind protocol considering that in previous studies this has been successfully done. Discussion -In my opinion, discussion should be partially rewritten. English writting should be improved as stated before. Also, given the lack of results (this is a protocol for a RCT) the discussion should focus on the strengths and limitations of the research protocol instead of doing a literature review (which was already done in the introduction). It could also discuss potential benefits that the authors expect to see after the intervention. Finally, with regard to the bibliography, some of the citations should be updated. If this paper includes patients with lung cancer the authors should mention the last Cochare systematic review published by Cavalheri and Granger. To sum up, this is a very interesting well-constructed research protocol with a large sample size and the results would most likely expand the current knowledge in lung cancer prehabilitation and will help with the implementation of this type of programmes. However, English should be improved and the discussion rewritten. I have attached the document with my comments and corrections if considered helpful.

REVIEWER	Catherine Granger The University of Melbourne, Australia
REVIEW RETURNED	03-Jul-2017

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. This paper describes the protocol of an RCT designed to investigate the impact of a home based 3 week pre-operative high intensive exercise program compared to usual care for patients with COPD going through resection for lung cancer. There are no published RCTs investigating this intervention delivered as a home program and thus this is a novel, important question. This topic is interesting and I believe would be of interest to readers particularly in light of the Cochrane review published this month specifically on pre-op exercise for lung cancer and the need for more high quality RCTs. The authors should be congratulated on planning to conduct this investigation. The main limitations are the English grammar making the paper hard to read, the lack of clear aims, insufficient details of the primary outcome measure/power calculation, details around measurement of other outcomes and the lack of proposed assessor blinding (which should be possible in this trial). I recommend the authors follow the SPIRIT guidelines to improve their paper. This is a great proposal and after amending the manuscript is worth publishing.

	Specific comments: - The English grammar could be improved throughout the abstract and manuscript. For example P1L39 “we will recruit 90 patients with Chronic Obstructive Pulmonary Disease diagnosed for lung cancer” – the use of ‘for’ does not make sense; P1L42 “A rehabilitation group (R group) will receive a standardized preoperative home exercise programme for 3 weeks, associating both high-intensity training and conventional physical therapy” – the use of the words ‘A’ and ‘associating’ is not correct.P5L18 “Study must investigate preoperative home rehabilitation in order to integrate patients better in their therapeutic project”. Please review the entire manuscript as the paper as it currently stands is difficult to read. - The abstract needs further detail around methodology – especially methods of randomisation, any form of blinding, timing of measurement - The outcome of ‘postoperative course’ could be more clearly defined in the abstract - The 10-item list for assessing discharge could be named in the abstract - The abstract states that the “The result of this original trial should confirm safety and feasibility of such short home-based interventions” yet there is no mention of safety or feasibility in the aims in the abstract. Please consider - The background section is missing an important new Cochrane review which has just been published (likely after this paper was submitted). Please include this reference: Cavalheri and Granger 2017 Cochrane – on this specific topic - The aims/objectives on p10 need to be clearer. What is the primary aim, what are the secondary aims? - The SPIRIT guidelines for protocols would be more appropriate than CONSORT to follow. Please review the SPIRIT guidelines and check compliance. Aspects are currently missing - Page 4 L 26 – this statement is correct but it needs a reference - Page 4 L 46 – “In consequence, a considerable number of patients require preoperative - optimization of respiratory and exercise capacity” is this statement a belief of the authors or can this be justified by a reference. Pre-op exercise training is not yet usual care so I am not sure this statement truly reflects current practice. Please revise. - P13 L37 – please clarify how many times the PT is going into the patients’ home. Is this 3 times per week for 3 weeks – this is not clear. Please revise - The term ‘realised’ is used incorrectly throughout the paper

	- This statement P9L44 is unclear “We will record the number of realized exercise session(s) effected, the number of exercise session(s) not effected and the reason(s) why they were not effected” – please rephrase - Description of the usual care in the control group needs more detail – where do these sessions occur? Is this in the home or hospital? Who prescribes and monitor this? Please include a description of usual care post-op physio as well. - The primary outcome measure needs stronger justification – please include references for this tool (I am not familiar with it) – is it valid and reliable, who completes it, when is it completed etc? Please provide more details. Please provide information on how post-op complications are measured – there are validated and reliable measurement tools for this purpose (the list on p28 does not look like a valid tool but if it is please justify its use and provide references) - Please confirm that repeat 6MWT will be conducted as per the ATS guidelines as there is a familiarisation effect for this test - Muscle strength – what sort of device are you using to measure this? What is the output measure/unit etc? - This type of study design does permit the assessors to be blinded. This is a major limitation in the proposal. Please consider having the assessors blinded to group allocation. - Why was the power calculation not performed not on the primary outcome measure? - It is unclear when all of the outcome measures are performed – please add - What is the current length of hospital stay for these patients are the hospital and therefore how feasible is the proposed 2 day reduction justified in the power calculation? - Figure 1 – please add the post-op outcomes including the primary measure in this figure

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1

In the text, with the exception of 1st, 6th and 11th days that will be supervised sessions, there is no information if the other days of training will be free choice of patients or if the study will determine the days.

Answer 1

Page 9, we added: “Non-supervised sessions will be performed during the week and not during the weekend to allow for email or phone contact with the physical therapist.”

Comment 2

Will upper limb exercises be performed on the same days as high intensity training? if yes, after or before? How will the load be determined? What exercises will be performed? What will be the number of repetitions and sets of the exercise?

Answer 2

We added limb exercises, page 9: “ Upper-arm exercises will be performed on the same days as after the cycling exercise. Muscles for shoulder (deltoid, pectoral and dorsal muscles), elbow (biceps and triceps muscles), wrist (flexors and extensors muscles) will be trained with elastics or dumbbells. For each muscle groups, 3-5 sets of 8-10 repetitions will be performed starting with the lowest resistance. Depending on the patient perception, the resistance will be increased.”

Reviewer: 2

Comment 1

Further, although the authors have stated that the English language has been verified by a native English translator, the authors should seek feedback from a native English speaker. Some sentences may have either lost their meaning during the translation process. One example is (page 9): “We will record the number of realized exercise session(s) effected, the number of exercise session(s) not effected and the reason(s) why they were not effected”.

Answer 1

We apologize for these errors and have now carefully reviewed the text. The English language has now been improved. It has been extensively reviewed by another professional editor.

Comment 2

Introduction

The gap in the literature was identified. However, some sentences in the introduction are vague and lack further explanation. Additionally, in several instances it is hard to the reader to understand the link between sentences. For instance, the flow of ideas presented between lines 22 and 48 can be improved by further explanation of thoughts as well as by using linking words to connect sentences.

Answer 2

We modified the introduction as you recommended. Please see the sentences in red pages 4- 6.

Comment 3

I have made some English language suggestion under “Specific comments”.

Answer 3

Thanks, we have integrated your suggestions in the manuscript.

Comment 4
Can the authors give a reason for why “only 25% of patients are considered suitable for surgery” (line 14; page 4)?

Answer 4
We completed this sentence as follows page 4: “However, only 25% of patients are considered suitable for surgery because of advanced-stage disease or poor functional status [4]”.

Comment 5
The aim stated at the end of the introduction does not match the aim stated in the abstract. The authors should state an aim that reflects their population, intervention and main outcomes. My suggestion is: “in people with lung cancer and COPD who are eligible for lung resection, to investigate the effectiveness of a home-based preoperative exercise training program on hospital discharge ability and postoperative complications”.

Answer 5
We modified the aim in the abstract as recommended and harmonized it in the introduction section. See the sentences in red page 1 and 6: “In light of the current literature, we implemented a multicentre RCT of an intensive 3-week preoperative home rehabilitation programme for COPD patients eligible for lung resection. We aim to confirm the effectiveness of a home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance.”

Comment 6
Methods
The methods are reasonably well described. The inclusion criteria are clear and specific. However, there is no need to state “>18 years old” as people are usually diagnosed with COPD when they are >40 years of age. The first two “non-inclusion criteria” are redundant as they are the opposite of two inclusion criteria.

Answer 6
In “2.2.1. inclusion criteria” page 7, we suppressed the >18 years old criteria; it was introduced for ethical purposes since we plan to include majors only.

Comment 7
People undergoing either lobectomy of pneumonectomy will be eligible for inclusion. What is not clear is the type of surgical approach. Will the study include people following VATS only, open thoracotomy only or either of these approaches?

Answer 7
This point has been specified as follows page 7: “Lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy)”.

Comment 8
Can the authors explain why the study will not include people living alone?

Answer 8
We will not include people living alone to ensure safety during the training sessions. This point was requested by our ethical committee. See: “2.2.2. Non-inclusion criteria” page 7: “Living alone at home (to ensure safety during the training sessions)”.

Comment 9
Can the authors clarify what they mean by “number of peaks”? The meaning of the term might have been lost with the translation to English language.

Answer 9
We changed the term “peaks” for “repetitons”. Please see modifications in red in the manuscript.

Comment 10
With respect to the muscle strengthening exercises for upper limbs using elastic bands, can the authors provide more details (i.e. how the intensity will be prescribed, how many days/week, which muscle groups will be the focus of the exercise prescription, sets, repetitions…) ?

Answer 10
This has now been detailed in the text in page 9: “Upper-arm exercises will be performed on the same days as after the cycling exercise. Muscles for shoulder (deltoid, pectoral and dorsal muscles), elbow (biceps and triceps muscles), wrist (flexors and extensors muscles) will be trained with elastics or dumbbells. For each muscle groups, 3-5 sets of 8-10 repetitions will be performed starting with the lowest resistance. Depending on the patient perception, the resistance will be increased.”

Comment 11
How will the authors measure adherence to the exercise intervention? Will patients be given a diary? Will the authors ring participants on a daily/weekly basis?

Answers 11
Please refer to the paragraph on page 9 “2.3.1. Rehabilitation group”: “The patient will complete a diary to collect the duration and intensity of the cycling exercise, mean HR and number of repetitons. We will record the number of exercise session(s) performed and the reason(s) for not performing exercise.”
Concerning adherence, please see page 14 “2.4.2.8. Feasibility and safety”: “To evaluate the feasibility of this protocol, we will consider recruitment and adherence rates [15]. Recruitment rate will be defined as the ratio of patients who agree to participate in the study to those who are eligible. Adherence rate will be defined as the ratio of the number of completed training sessions to the number of expected sessions. Adherence will be considered acceptable with performance of 11 of the 15 expected exercise sessions. Adverse events will be systematically tracked during the study period and follow-up.”

Comment 12
The authors will be conducting an impressive number of assessments. What is not clear is the number of assessment days that will be required at each evaluation period. Can the authors give specific details of number of assessment days, which assessments will be performed on the same day and what is the rest period between one assessment day and the next? The concern is the high burden all these assessment will have on participants of the study.

Answer 12
The physical and body composition evaluations will be scheduled on the same day. All these tests require about 2 hours per patient and will be performed in the same clinical physiology lab. For details, please see the following paragraph on page 10.
See: “Participants will undergo all assessments in the physiology laboratory on the same day so as to limit transport and fatigue. Baseline assessments will be performed 1 month before surgery (pre-intervention or first evaluation) and will be renewed the day before surgery (post-intervention or second evaluation).

To ensure reproductibility of the assessments, the order will be standardized: pulmonary function tests, maximal respiratory pressure measurements, cardiopulmonary exercise test, 6-min walk test (6MWT), bioimpedancemetry, maximum voluntary isometric quadriceps strength measurement and quality of life. The rest period will be respected according to patients' needs."

Comment 13
Hospital discharge ability: was the 10-item list developed by the research group? Is it currently used in the 4 hospitals where participants will be recruited from? Has it been validated?

Answer 13
Our 10-item list assessing hospital discharge ability was developed by a panel of caregivers (surgeons, physiologists, physical medicine physician and physical therapists). We acknowledge that this criteria is not validated in a published study. Clinical practice demonstrates that the hospital length of stay is influenced by extra medical parameters (social, post-operative care organization etc). We listed the clinical criteria used by thoracic surgeons in our trial to determine the patient's discharge. This allowed for developing this 10-item list. We plan to compare this discharge ability criteria to the true hospital length of stay. This will allow for fully validating our criteria. See red color in "2.4.1. Primary outcome" page 10-11.

Comment 14
For all outcome measures described, please include the devices that will be used to measure them as well as the devices' model and manufacturer details.

Answer 14
This has been specified in the corresponding paragraphs of the methods section in red.

Comment 15
If data from PFT, maximal respiratory pressures, CPET, 6MWT and quads strength will be presented using absolute values as well as a percentage of predicted values, please provide references for the studies in which the predicted values have been published.

Answer 15
This has been specified in the text. We added reference values for PFT [20], maximal respiratory pressures [23], CPET [25], 6MWT [27] and quadriceps strength [32].

Comment 16
CPET - What will be the initial workload? What about the workload for the one-minute increments?

Answer 16
See modification in "2.4.2.3. Cardiopulmonary exercise test (CPET)" page 12: "The workload increments will be defined according to predicted maximal power output (Wmax), with a first stage of warm-up corresponding to 30% Wmax and 10 following stages to complete the test in 12 to 15 min. "

Comment 17
6MWT – It is well known that the 6MWT has a learning effect. Will the participants undergo 2 6MWT's during the first evaluation period? If so, how long will they rest between the first and second 6MWT?

Answer 17
We confirm that the 6MWT will be conducted as per the ATS guidelines [26]. We acknowledge that the 6MWT has a learning effect but we chose to limit the evaluations performed at every visit. Since we included only COPD patients, most will have already performed 6MWTs. So, this learning effect should be minimized.

We chose not to perform 2 6MWTs during the first evaluation because of the high burden all these assessments will have on participants. We chose to favour participants' adherence and motivation for exercise as well. Thus, we paid special attention to the explanations and the order delivered before the 6MWT. Additionally, there is a well-shown correlation between field tests (6MWT, ISWT and ESWT) and CPET [26].

Comment 18
Randomization and allocation – The randomization sequence should be generated/managed by someone who is not involved in the research. Not by the research manager. Also, can the authors give more details about the allocation concealment?

Answer 18
We modified the sentence as follows on page 14 and 15: "The randomization sequence will be generated and managed electronically by a research manager independent of assessments or interventions. Allocation will be transmitted by emails send to all assessors and therapists involved. Allocation concealment is not possible in such an exercise training trial, and especially in a multicentre study, the physical evaluation and intervention could not be blinded."

Comment 19
Discussion
Can the authors elaborate more on the mechanism behind decreased postoperative complications and length of stay due to improvements in preoperative exercise capacity? That is, why would an improvement in preoperative exercise capacity lead to improved postoperative outcomes?

Answer 19
This point has been clarified in the discussion section (page 17 and 18).
Please see red: "Mechanisms underlying decreased hospital discharge ability or postoperative complication rate need further investigation. Nevertheless, VO2peak is the strongest independent predictor of surgical complications and survival rates in NSCLC [6]. We hypothesize that increasing pre-surgical physical fitness and VO2peak should decrease hospital length of stay, postoperative complications and mortality in this population. Moreover, recent systematic reviews demonstrated these important outcomes [9–11]. Even more, a home-based programme should improve adherence to the programme without delaying the surgical treatment. Despite a short time course, the effectiveness of preoperative physical conditioning would increase and could explain the benefits on morbidity. "
Similarly, we developed a specific paragraph for the strengths and limitations of our study.

Comment 20
Specific comments and English language tips
Abstract: Conclusion – Delete the" from "We hypothesize … will increase the aerobic capacity"
Introduction: Page 4 (line 9): "surgery is conducted in a curative intent" – replace "in" with "with"; (line 11): "early TNM disease stages (stages I and II)" – include (stages I, II and IIIA); (line 27): "Patients with complicated postoperative course have a longer hospital length of stay, a more frequent stay in intensive care unit (ICU) and a higher mortality rate" – please include reference for this statement; (line 33): "Field tests are…" include "Performance during field-based tests are…"; (line 37): "Surgery itself initiates…" replace "initiates" with "leads to".
Page 5 (line 5): "Two recent systematic reviews reported…", please have a look at a recently published Cochrane review on preoperative exercise training in people with lung cancer;
Methods: Page 8 (line 33): "The Rehabilitation group will realize…" – replace "realize" with "undergo"; (line 55): "ability to complete his training course and to teach him" – replace "his" with "their" and replace "him" with "them".
Page 11 (line 50): "It will be realized…" – replace "realized" with "performed"

Page 14 (line 9): “… those who realize…” – replace “realize” with “attended”.
Page 16 (line 3): “This analysis will be performed intent-to-treat” – reword to “This analysis will be performed according to the intention-to-treat principle”.

Answer 20
We took into account your suggestions for English language. Thanks.
We also mentioned the last Cochrane systematic review published recently by Cavalheri and Granger [11], which was published after the initial submission.

Reviewer: 3
This is a very interesting study which will address very important outcomes for clinical practice in patients with lung cancer. One of the strengths of this research piece is the elevated number of patients which will be recruited (over 90) and the fact that it will be short (three weeks) and minimally supervised (one session at the hospital two unsupervised at home) which will probably improve the recruitment rate and completion rate (which is usually pretty low in this type of patients).

Comment 1
However, at the moment the study present some limitations that must be addressed before acceptance. For starters, the authors say that the English has been proofread by a native speaker but I strongly disagree since I have noticed several grammatical mistakes and some sentences and even paragraphs should be rewritten. For example, in the abstract it says "was shown" instead of have shown; they also used somewhere realized instead of performed; the article "the" is constantly used when it shouldn't be, and so on. More examples of this can be found in page 4 line 16 and 26-27; in the inclusion criteria it should read predicted not theoretical; page 8 line 44; page 9 lines 20 to 25... Also, they are apparently writing in British English but some other words such as dyspnoea and post-operative complications are written correspond to American English. Please unify.

Answer 1
We apologize for these errors and have now carefully reviewed the text. The English language has now been improved. It has been extensively reviewed by another professional editor.

Comment 2
When the authors say contraindication to perform CPET could they be more specific?

Answer 2
Please see page 7: “Contraindication to surgery based on the initial cardiopulmonary exercise test (CPET)” or “Cardiac or vascular contraindication to the rehabilitation programme”.
The first criteria refers to a poor exercise performance (predicted postoperative VO2peak <12 ml/kg/min) which is a validated contraindication criteria to surgery in these patients. The second one corresponds to cardiac ischemia or severe arrhythmias revealed during CPET.

Comment 3
The standard care should be described in detail. For instance, they say global training what does that mean? Endurance training? Which type/intensity/frequency....?

Answer 3
We described more precisely this point page 9 and 10. Please see “2.3.2. Control group”: “ A control group (C group) will perform 15 standardized preoperative physical therapy sessions according to usual care. The sessions will consist in 30 min performed 5 days/week for 3 weeks. They will be standardized with a written prescription and will include airway clearance techniques, deep breathing exercises emphasizing inspiration, thoracic stretching and upper- and lower-limb stretching. According to current recommendations, the C group will be advised to be physically active.”

Comment 4
More information is needed regarding surgery. What approach is going to be performed? This should also be stated because it will affect the post-operative course

Answer 4
Please see modification of “2.2.1. Inclusion criteria” page 7: “Lung cancer (or high suspicion for malignant tumour) eligible for resection surgery (lobectomy or pneumonectomy with video-assisted thoracic surgery or open thoracotomy)”.

Comment 5
With regard to the methodology, I don't understand why the authors say that this can't be an assesor-blind protocol considering that in previous studies this has been successfully done.

Answer 5
Please see “2.7. Masking and blinding” for modifications page 15: “In such a clinical experiment, blinding is not possible for patients and caregivers or assessors. However, the C group receiving only usual care will allow for demonstrating the beneficial effect of the intervention in the R group. To limit bias, we will ensure that assessors and caregivers will be different during the trial period. Moreover, we will ensure that participants do not meet each other.”

Comment 6
Discussion
In my opinion, discussion should be partially rewritten. English writting should be improved as stated before. Also, given the lack of results (this is a protocol for a RCT) the discussion should focus on the strengths and limitations of the research protocol instead of doing a literature review (which was already done in the introduction). It could also discuss potential benefits that the authors expect to see after the intervention.
Finally, with regard to the bibliography, some of the citations should be updated. If this paper includes patients with lung cancer the authors should mention the last Cochare systematic review published by Cavalheri and Granger.
To sum up, this is a very interesting well-constructed research protocol with a large sample size and the results would most likely expand the current knowledge in lung cancer prehabilitation and will help with the implementation of this type of programmes. However, English should be improved and the discussion rewritten. I have attached the document with my comments and corrections if considered helpful.

Answer 6
We modified discussion as advised. Please see page 17 and 18. We developed the strengths and limitations and potential mechanisms underlying the benefits that should explain the expected results. We also mentioned the last Cochrane systematic review published recently by Cavalheri and Granger [11], which was published after the initial submission.

Reviewer: 4

Comment 1

Thank you for the opportunity to review this manuscript. This paper describes the protocol of an RCT designed to investigate the impact of a home based 3 week pre-operative high intensive exercise program compared to usual care for patients with COPD going through resection for lung cancer. There are no published RCTs investigating this intervention delivered as a home program and thus this is a novel, important question. This topic is interesting and I believe would be of interest to readers particularly in light of the Cochrane review published this month specifically on pre-op exercise for lung cancer and the need for more high quality RCTs. The authors should be congratulated on planning to conduct this investigation.

The main limitations are the English grammar making the paper hard to read, the lack of clear aims, insufficient details of the primary outcome measure/power calculation, details around measurement of other outcomes and the lack of proposed assessor blinding (which should be possible in this trial). I recommend the authors follow the SPIRIT guidelines to improve their paper. This is a great proposal and after amending the manuscript is worth publishing.

Answer 1

We apologize for these errors and have now carefully reviewed the text. The English language has now been improved. It has been extensively reviewed by another professional editor.

We mentioned the last Cochrane systematic review published recently by Cavalheri and Granger [11], which was published after the initial submission.

We rewrote the aim of the study in the abstract and in the introduction. Please see red color in corresponding sections page 1 and 6: “In light of the current literature, we implemented a multicentre RCT of an intensive 3-week preoperative home rehabilitation programme for COPD patients eligible for lung resection. We aim to confirm the effectiveness of a home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance.”

The size of the sample has been calculated as specified on page 15 using the hospital length of stay published in previous studies [36, 37]. Because our primary outcome criteria has never been used before, we cannot adjust the power size calculation on it. However, if the discharge ability is significantly different from the true hospital length of stay, the difference should be similar in the two groups and should not influence our conclusions.

We gave details about measurements of primary and secondary outcomes (materials) and considered predicted values for PFT, maximal respiratory pressures, CPET, 6WMT and quadriceps strength. Please see the modified sentences in red and reference values for PFT [20], maximal respiratory pressures [23], CPET [25], 6MWT [27] and quadriceps strength [32].

Regarding to assessor-blinding, please see “2.7. Masking and blinding” page 15: “In such a clinical experiment, blinding is not possible for patients and caregivers or assessors. However, the C group receiving only usual care will allow for demonstrating the beneficial effect of the intervention in the R group. To limit bias, we will ensure that assessors and caregivers will be different during the trial period. Moreover, we will ensure that participants do not meet each other.”

For Spirit guidelines, please see the specific answer below.

Specific comments:

Comment 2

The English grammar could be improved throughout the abstract and manuscript. For example P1L39 “we will recruit 90 patients with Chronic Obstructive Pulmonary Disease diagnosed for lung cancer” – the use of ‘for’ does not make sense; P1L42 “A rehabilitation group (R group) will receive a standardized preoperative home exercise programme for 3 weeks, associating both high-intensity training and conventional physical therapy” – the use of the words ‘A’ and ‘associating’ is not correct.

P5L18 “Study must investigate preoperative home rehabilitation in order to integrate patients better in their therapeutic project”. Please review the entire manuscript as the paper as it currently stands is difficult to read.

Answer 2
We apologize for these errors and have now carefully reviewed the text. The English language has now been improved. It has been extensively reviewed by another professional editor.
The sentences have been modified as suggested. Thanks for your suggestions.

Comment 3
The abstract needs further detail around methodology – especially methods of randomisation, any form of blinding, timing of measurement

Answer 3
We modified the abstract page 1 and 2. Please see red: “The randomization sequence will be generated and managed electronically by a research manager independent of assessments or interventions” and “… assessed 1 month before and the day before surgery.”

Comment 4
The outcome of ‘postoperative course’ could be more clearly defined in the abstract

Answer 4
The postoperative course has been more clearly defined in the abstract page 1. See red: “(complication rate and mortality)”

Comment 5
The 10-item list for assessing discharge could be named in the abstract

Answer 5
We identified our 10-item list assessing hospital discharge ability in the abstract page 1. See red: “hospital discharge ability assessed with a 10-item list.”

Comment 6
The abstract states that the “The result of this original trial should confirm safety and feasibility of such short home-based interventions” yet there is no mention of safety or feasibility in the aims in the abstract. Please consider

Answer 6
We modified the abstract page 2: “The results of this original multicentre randomized trial of home-based rehabilitation should confirm the effectiveness of a short intensive home-based intervention for COPD patients eligible for lung cancer surgery. They could change practice before lung cancer resection thereby enabling preconditioning without delaying surgical treatment.”

Comment 7
The background section is missing an important new Cochrane review which has just been published (likely after this paper was submitted). Please include this reference: Cavalheri and Granger 2017 Cochrane – on this specific topic

Answer 7
In the introduction and background sections, we added the new Cochrane review which was published after the initial submission. See page 4 and 5: “A recent Cochrane review emphasized the need for larger high-quality randomized controlled trials (RCTs) in this area and the disparities between studies [11].”

Comment 8
The aims/objectives on p10 need to be clearer. What is the primary aim, what are the secondary aims?

Answer 8
The aim has been clarified in the abstract and in the introduction sections page 1 and 6. See the sentences in red that have been modified to state the primary and secondary aims.

Comment 9
The SPIRIT guidelines for protocols would be more appropriate than CONSORT to follow. Please review the SPIRIT guidelines and check compliance. Aspects are currently missing

Answer 9
We conduct this trial in accordance with the Consort recommendations for non-pharmacological trials. We use the Consort checklist for reporting trials of non-pharmacologic treatments, which is to our knowledge the most adapted for describing an exercise intervention (Boutron I, Moher D, Altman DG, Schulz KF, Ravaud P, CONSORT Group. Methods and processes of the CONSORT Group: example of an extension for trials assessing nonpharmacologic treatments. Ann Intern Med 2008; 148(4): W60-66.) [34].

Comment 10
Page 4 L 26 – this statement is correct but it needs a reference

Answer 10
We included a reference supporting this statement page 4. See: “Patients with a complicated postoperative course have a longer hospital length of stay, more frequent stay in an intensive care unit (ICU) and higher mortality rate [5].”

Comment 11
Page 4 L 46 – “In consequence, a considerable number of patients require preoperative optimization of respiratory and exercise capacity” is this statement a belief of the authors or can this be justified by a reference. Pre-op exercise training is not yet usual care so I am not sure this statement truly reflects current practice. Please revise.

Answer 11
We acknowledge that this statement was not supported by published data and we removed it.

Comment 12
P13 L37 – please clarify how many times the PT is going into the patients’ home. Is this 3 times per week for 3 weeks – this is not clear. Please revise

Answer 12
This has been detailed in page 9 and 10: " A control group (C group) will perform 15 standardized preoperative physical therapy sessions according to usual care. The sessions will consist in 30 min performed 5 days/week for 3 weeks. They will be standardized with a written prescription and will include airway clearance techniques, deep breathing exercises emphasizing inspiration, thoracic stretching and upper- and lower-limb stretching. According to current recommendations, the C group will be advised to be physically active."

Comment 13
The term 'realised' is used incorrectly throughout the paper

Answer 13
The term "realised" has been changed to "performed".

Comment 14
This statement P9L44 is unclear "We will record the number of realized exercise session(s) effected, the number of exercise session(s) not effected and the reason(s) why they were not effected" – please rephrase

Answer 14
We clarified and rephrased. See page 9: "The patient will complete a diary to collect the duration and intensity of the cycling exercise, mean HR and number of repetitons. We will record the number of exercise session(s) performed and the reason(s) for not performing exercise. "

Comment 15
Description of the usual care in the control group needs more detail – where do these sessions occur? Is this in the home or hospital? Who prescribes and monitor this? Please include a description of usual care post-op physio as well.

Answer 15
We developed this. See "2.3.2. Control group": "A control group (C group) will perform 15 standardized preoperative physical therapy sessions according to usual care. The sessions will consist in 30 min performed 5 days/week for 3 weeks. They will be standardized with a written prescription and will include airway clearance techniques, deep breathing exercises emphasizing inspiration, thoracic stretching and upper- and lower-limb stretching. According to current recommendations, the C group will be advised to be physically active."

Comment 16
The primary outcome measure needs stronger justification – please include references for this tool (I am not familiar with it) – is it valid and reliable, who completes it, when is it completed etc? Please provide more details.
Please provide information on how post-op complications are measured – there are validated and reliable measurement tools for this purpose (the list on p28 does not look like a valid tool but if it is please justify its use and provide references)

Answer 16
Concerning our primary outcome, we further defined it. Our 10-item list assessing hospital discharge ability was developed by a panel of caregivers (surgeons, physiologists, physical medicine physician and physical therapists). We acknowledge that this criteria is not validated in a published study. Clinical practice demonstrates that the hospital length of stay is influenced by extra medical parameters (social, post-operative care organization etc). We listed the clinical criteria used by thoracic surgeons in our trial to determine the patient's discharge.

This allowed for developing this 10-item list. We plan to compare this discharge ability criteria to the true hospital length of stay. This will allow for fully validating our criteria. See red in “2.4.1. Primary outcome” page 10 and 11.
Concerning to postoperative complications, we added references for definitions. See: references [17,18]. Also, we defined the data collection management. See “2.4.2.1. Postoperative course” page 11: “The postoperative course will be assessed daily by the thoracic surgeon and by information from the patient's file.”

Comment 17
Please confirm that repeat 6MWT will be conducted as per the ATS guidelines as there is a familiarisation effect for this test

Answer 17
We confirm that the 6MWT will be conducted as per the ATS guidelines [26]. We acknowledge that the 6MWT has a learning effect but we chose to limit the evaluations performed at every visit. Since we included only COPD patients, most will have already performed 6MWTs. So, this learning effect should be minimized.
We chose not to perform 2 6MWTs during the first evaluation because of the high burden all these assessments will have on participants. We chose to favour participants’ adherence and motivation for exercise as well. Thus, we paid special attention to the explanations and the order delivered before the 6MWT. Additionally, there is a well-shown correlation between field tests (6MWT, ISWT and ESWT) and CPET [26].

Comment 18
Muscle strength – what sort of device are you using to measure this? What is the output measure/unit etc?

Answer 18
We used a Dynatrac strain-gauge. See modification page 13 in red in “2.4.2.6. Maximum voluntary isometric quadriceps strength”. The result will be in kilograms.

Comment 19
This type of study design does permit the assessors to be blinded. This is a major limitation in the proposal. Please consider having the assessors blinded to group allocation.

Answer 19
Please see “2.7. Masking and blinding” page 15: “In such a clinical experiment, blinding is not possible for patients and caregivers or assessors. However, the C group receiving only usual care will allow for demonstrating the beneficial effect of the intervention in the R group. To limit bias, we will ensure that assessors and caregivers will be different during the trial period. Moreover, we will ensure that participants do not meet each other.”

Comment 20
Why was the power calculation not performed not on the primary outcome measure?

Answer 20
To our knowledge it is the first time that hospital discharge ability was used as primary outcome in this setting.
The mean hospital length of stay in our thoracic surgery department was 8.8 days in 2016. In the last Cochrane review [11], the mean hospital length of stay was 10 to 12 days in control groups and the mean effect of exercise training was a reduction of 4 days. The actual length of stay is lower in our department but the targeted reduction is only 2 days. So, we feel confident that our objective could be fulfilled with the planned exercise training programme.

Comment 21
It is unclear when all of the outcome measures are performed – please add

Answer 21
For precision see red in “Primary and secondary outcomes measures and assessment point” page 10: “Participants will undergo all assessments in the physiology laboratory on the same day so as to limit transport and fatigue. Baseline assessments will be performed 1 month before surgery (pre-intervention or first evaluation) and will be renewed the day before surgery (post-intervention or second evaluation). To ensure reproductibility of the assessments, the order will be standardized: pulmonary function tests, maximal respiratory pressure measurements, cardiopulmonary exercise test, 6-min walk test (6MWT), bioimpedancemetry, maximum voluntary isometric quadriceps strength measurement and quality of life. The rest period will be respected according to patients’ needs.”

Comment 22
What is the current length of hospital stay for these patients are the hospital and therefore how feasible is the proposed 2 day reduction justified in the power calculation?

Answer 22
Please see answer 20 for explanation.

Comment 23
Figure 1 – please add the post-op outcomes including the primary measure in this figure

Answer 23
We added our primary outcome and postoperative outcomes in figure 1.

VERSION 2 – REVIEW

REVIEWER	Dr Vinicius Cavalheri School of Physiotherapy and Exercise Science, Curtin University, Australia
REVIEW RETURNED	08-Sep-2017

GENERAL COMMENTS	It was a pleasure to review this protocol. The new version has improved substantially and reads really well. You have done a great job. One minor comment from me - twice in the paper the word "pulmonary" has been typed "pulmponary". I am looking forward to the findings of your RCT. Best regards,

REVIEWER	Raquel Sebio School of Health Sciences. TecnoCampus. University Pompeu Fabra. Mataró (Spain)
REVIEW RETURNED	13-Sep-2017

GENERAL COMMENTS	The authors have improved the English writing and it is now appropriate for publication. There are only few minor spelling errors that I'll address in the corresponding sections. Still some discrepancies between British and American English. For instance, they say programme (British) but then they write dyspnea (American). ESPECIFIC COMMENTS: INTRODUCTION Introduction has been improved and the literature review is updated. However, I believe it is maybe too long and it should be shortened and more concise. METHODS -Line 47-8 page 7: in the contraindications for surgery, after "based on the initial results of the CPET", the authors should include the latest reference to be clear about the specific contraindications. -Line 10 page 8: I'll substitute pregnant for pregnancy. -Line 25: rewrite the sentence. It doesn't seem clear to me if the supervised sessions are on three consecutive days, or on non-consecutive days or if they're all performed on the same day (writing is confusing). -Line 41 page 9: delete "as". Also, will be any rest between the endurance and the strength training? If so, of how long? -Line 42: change "muscles for" and use instead "shoulder (...),elbow (...) and wrist (...) muscles will be trained...". It's not clear to me how the training intensity will be established. The authors say that the progression will be perception-related but which intensity will be set as the inicial target? Will intensity be determined with a Borg Scale or any other standardised tool? I suggest the OMNI-res scale as it has been validated to use with elastic bands (Colado et al., 2012). -Line 5 page 10: change consist in for "consist of" -Same line says: "30 minutes", but 30 minutes of what? Is it referring to the whole session? If so, please rewrite to make it clearer. -Line 38-39: substitute renewed for "repeated" -I highly suggest the authors of the study to specify rest duration between tests, or at least specify how they will make sure that the patient is ready to continue with the evaluations. Otherwise it will be very difficult to not consider this as a potential bias in the study (performance in the different tests will differ depending on the baseline status of the patient when conducting the test). For example, between the 6MWT and the CPET a minimum of 30-45 minutes should be encouraged. Check the literature for recommendations.

	-Line 12 page 11: substitute independent for "non-related" -Masking/Blinding: it is still not clear to me why the assessors can't be blinded. If the authors say that the caregivers and/or those supervising the exercise programme are not the same as the assessors, I don't see why the latter can't be blinded of the allocation of the patients since it will definitely reduced the risk of bias. Otherwise, the assessor can be influenced when conducting the test by the allocation group. Maybe a third person not involved in the study can join the investigation in each center to perform the post-intervention evaluations at least for the main study endpoint. DISCUSSION Discussion is adequate and updated but maybe a little scarce comparing to the introduction CONCLUSION I suggest changing "should confirm" in line 7 for "could strengthen" given that it is still not clear if the intervention would be effective (that's why it is an hypothesis).

REVIEWER	Catherine Granger The University of Melbourne
REVIEW RETURNED	09-Sep-2017

GENERAL COMMENTS	Thank you for the opportunity to review the revision of this manuscript. This paper describes the protocol of an RCT designed to investigate the impact of a home based 3 week pre-operative high intensive exercise program compared to usual care for patients with COPD going through resection for lung cancer. The authors should be congratulated on the revisions to this paper. In particular the English grammar is significantly better. I only have a couple of very minor suggestions: - Page 104 – strengths and limitations section- the dot point stating 'no blinding' should be expanded into a sentence and clarify there is no assessor or patient blinding - Please clarify the term 'caregiver' -For example page 116 L27 " To limit bias, we will ensure that assessors and caregivers will be different during the trial period" – this sentence does not make sense. Please re-consider this whole sentence, plus review where the term 'caregiver' occurs in the paper and check this is what you mean. - P118 L52 "We acknowledge that the main limitation of our study is that patients and assessors will not be blinded to the intervention arm. However, we will ensure that assessors and therapists will be different during the trial period" - Please clarify the expected benefit of using different assessors and therapists during the trial period – this does not reduce the bias of not having blinding. - Aims: please consider changing the word 'confirm' to 'investigate' or 'determine' throughout the entire paper ("We aim to confirm the effectiveness of a home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance)

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Comment 1
Dear Helene Laurent and colleagues,
It was a pleasure to review this protocol. The new version has improved substantially and reads really well. You have done a great job.
One minor comment from me - twice in the paper the word "pulmonary" has been typed "pulmponary".
I am looking forward to the findings of your RCT.
Best regards,
Vin

Answer 1
Thank you for your comment and encouragements. The typewritting errors in ‘pulmonary’ have been corrected.

Reviewer: 3
OVERALL COMMENT
Comment 1
The authors have improved the English writing and it is now appropriate for publication. There are only few minor spelling errors that I'll address in the corresponding sections. Still some discrepancies between British and American English. For instance, they say programme (British) but then they write dyspnea (American).

Answer 1
We changed it.
SPECIFIC COMMENTS
INTRODUCTION

Comment 2
Introduction has been improved and the literature review is updated. However, I believe it is maybe too long and it should be shortened and more concise.

Answer 2
We shortened and concised the introduction. Please see the relative section.
METHODS

Comment 3
-Line 47-8 page 7: in the contraindications for surgery, after "based on the initial results of the CPET", the authors should include the latest reference to be clear about the specific contraindications.

Answer 3
We included the lastest ACCP guidelines on the physiological assessement before surgery of patients with lung cancer ([6]. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143(5 Suppl): e166S-190S).

Comment 4
-Line 10 page 8: I'll substitute pregnant for pregnancy.

Answser 4
We substituted "pregnant" for "pregnancy".

Comment 5
-Line 25: rewrite the sentence. It doesn't seem clear to me if the supervised sessions are on three consecutive days, or on non-consecutive days or if they're all performed on the same day (writing is confusing).

Answer 5
We rewrote the sentences: "Over 3 weeks, the patients will perform 15 sessions of rehabilitation (5 days/week) including 1 supervised session performed per week" and "A physical therapist experienced in pulmonary rehabilitation will visit the patient at home and supervise one session per week (at the beginning of each of the three weeks: the 1st, 6th and 11th exercise session)". Please see red in "2.3.1. Rehabilitation group".

Comment 6
-Line 41 page 9: delete "as". Also, will be any rest between the endurance and the strength training? If so, of how long?

Answer 6
We deletes "as".
Also, we precised: "A rest duration of at least 45 min will be respected between CPET and 6MWT". Please see red.

Comment 7
-Line 42: change "muscles for" and use instead "shoulder (...),elbow (...) and wrist (...) muscles will be trained...". It's not clear to me how the training intensity will be established. The authors say that the progression will be perception-related but which intensity will be set as the inicial target? Will intensity be determined with a Borg Scale or any other standardised tool? I suggest the OMNI-res scale as it has been validated to use with elastic bands (Colado et al., 2012).

Answer 7
We changed and used "Shoulder (deltoid, pectoral and dorsal muscles), elbow (biceps and triceps muscles), wrist (flexors and extensors muscles) muscles will be trained with elastics or dumbbells". We acknowlegde that the intensity and the progression of resistance training with elestic bands are poorly standardized. However, in this setting (home based) in middle-aged and elderly patients, we do not plan an actual resistance training programme but rather muscle reinforcement. Our primary objective is to increase aerobic capacity and not muscle strength. Consequently, it does not seem realistic to impose an additional measurement of patients' sensations. When necessary, the resistance of the elastic bands will be adjusted weekly during the supervised training session. Moreover, you suggested to use the OMNI-res scale developped by Colado et al in 2012. This scale was validated in a limited sample of young and very active healthy subjects. Then, we have no strong evidence that this scale could be adapted to our population of deconditioned and older patients.

Comment 8
-Line 5 page 10: change consist in for "consist of"

Answer 8
We changed for "consist of".

Comment 9
-Same line says: "30 minutes", but 30 minutes of what? Is it referring to the whole session? If so, please rewrite to make it clearer.

Answer 9
We rewrote: "The sessions will consist of 30 min of standardized preoperative physical therapy performed 5 days/week for 3 weeks". Please see red.

Comment 10
-Line 38-39: substitute renewed for "repeated"

Answer 10
We substituted for "repeated".

Comment 11
-I highly suggest the authors of the study to specify rest duration between tests, or at least specify how they will make sure that the patient is ready to continue with the evaluations. Otherwise it will be very difficult to not consider this as a potential bias in the study (performance in the different tests will differ depending on the baseline status of the patient when conducting the test). For example, between the 6MWT and the CPET a minimum of 30-45 minutes should be encouraged. Check the literature for recommendations.

Answer 11
We acknowledge we should respect rest periods between fonctional capacity tests. We precised in the text that CPET and 6MWT will be be separated by at least 45 min. In the work schedule, we plan to spend these resting periods to fill in quality of life questionnaires.

Comment 12
-Line 12 page 11: substitute independent for "non-related"

Answer 12
We changed for "non-related".

Comment 13
-Masking/Blinding: it is still not clear to me why the assessors can't be blinded. If the authors say that the caregivers and/or those supervising the exercise programme are not the same as the assessors, I don't see why the latter can't be blinded of the allocation of the patients since it will definitely reduced the risk of bias. Otherwise, the assessor can be influenced when conducting the test by the allocation group. Maybe a third person not involved in the study can join the investigation in each center to perform the post-intervention evaluations at least for the main study endpoint.

Answer 13
From a pratical point of view, we cannot impose on the patients to do not disclose their allocation group. So, we think that any attempt to blind the assessors will not be successful.
Regarding maximal exercise testing which is one the secondary objectives, assessors in charge of this test are physicians trained in exercise physiology. Since, peak VO2 is a strong predictor of postoperative outcome we feel confident that the assessors will encourage every patients, whatever his allocation group, to their maximum in order to obtain a valuable measurement.
DISCUSSION

Comment 14
Discussion is adequate and updated but maybe a little scarce comparing to the introduction

Answer 14
We improved the discussion section like you recommended.
CONCLUSION

Comment 15
I suggest changing "should confirm" in line 7 for "could strengthen" given that it is still not clear if the intervention would be effective (that's why it is an hypothesis).

Answer 15
We changed it as suggested.

Reviewer: 4
Thank you for the opportunity to review the revision of this manuscript. This paper describes the protocol of an RCT designed to investigate the impact of a home based 3 week pre-operative high intensive exercise program compared to usual care for patients with COPD going through resection for lung cancer. The authors should be congratulated on the revisions to this paper. In particular the English grammar is significantly better. I only have a couple of very minor suggestions

Comment 1
- Page 104 – strengths and limitations section- the dot point stating ‘no blinding’ should be expanded into a sentence and clarify there is no assessor or patient blinding

Answer 1
We modified for "There is no assessor or patient blinding".

Comment 2
- Please clarify the term ‘caregiver’ -For example page 116 L27 “ To limit bias, we will ensure that assessors and caregivers will be different during the trial period” – this sentence does not make sense. Please re-consider this whole sentence, plus review where the term ‘caregiver’ occurs in the paper and check this is what you mean.

Answer 2
We changed for "therapists". Please see red.

Comment 3
- P118 L52 “We acknowledge that the main limitation of our study is that patients and assessors will not be blinded to the intervention arm. However, we will ensure that assessors and therapists will be different during the trial period”- Please clarify the expected benefit of using different assessors and therapists during the trial period- this does not reduce the bias of not having blinding.

Answer 3
We acknowledge that our unblinded procedure do not eliminate the risk of bias. In such exercise training programmes, a blinding procedure for the experimentators is uncommon. Since we cannot impose on the patients to do not disclose their allocation group, a blinding of assessors does not seem applicable. It seems to us that it will be the "least bad" organization to reduce the bias.

Comment 4
- Aims: please consider changing the word ‘confirm’ to ‘investigate’ or ‘determine’ throughout the entire paper (“We aim to confirm the effectiveness of a home-based preoperative exercise training programme on hospital discharge ability, postoperative complications and physical performance)

Answer 4
We changed for "investigate".

VERSION 3 – REVIEW

REVIEWER	Raquel Sebio School of Health Sciences. TecnoCampus. University Pompeu Fabra. Barcelona (SPAIN)
REVIEW RETURNED	25-Sep-2017

GENERAL COMMENTS	The authors have reviewed the manuscript according the reviewer's comments and the article is now ready for publication. I am looking forward to the results of this randomized, multicenter controlled trial.

REVIEWER	Dr Catherine Granger The University of Melbourne
REVIEW RETURNED	26-Sep-2017

GENERAL COMMENTS	Thank you for your changes.